Clinical trial results:
Pre-emptive therapy of acute graft versus host disease according to specific proteomic patterns after allogeneic hematopoietic stem cell transplantation.

Summary

EudraCT number	2008-005862-30
Trial protocol	DE
Global end of trial date	07 December 2015

Results information

Result version number	v1 (current)
This version publication date	19 January 2024
First version publication date	19 January 2024

Trial information

Trial identification

Sponsor protocol code	MHH-Pre-GvHD-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hannover Medical School
Sponsor organisation address	Carl-Neuberg-Str. 1, Hannover, Germany, 30625
Public contact	Stabsstelle Zentrum für Klinische Forschung, Hannover Medical School, EudraCT@mh-hannover.de
Scientific contact	Stabsstelle Zentrum für Klinische Forschung, Hannover Medical School, EudraCT@mh-hannover.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 December 2015
Global end of trial reached?	Yes
Global end of trial date	07 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To test the efficacy of pre-emptive immunosuppressive treatment (2-2.5mg prednisolone/kg BW/day) versus placebo immediately when a positive acute Graft-versus-Host disease (aGvHD,grade II-IV) and a specific proteomic pattern is observed.

Protection of trial subjects:

The clinical trial was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and with the standards of International Conference on Harmonisation (ICH) Good Clinical Practice (GCP). A continuous risk assessment was performed during the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 259
Worldwide total number of subjects	259
EEA total number of subjects	259

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	233
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

260 patients after allogeneic hematopoietic stem cell transplantation (allo-HSCT) for hematologic malignancies or dysfunction syndromes were to be included in the clinical trial.

Pre-assignment

Screening details:

Eligibility will be determined based upon the inclusion and exclusion criteria

Period 1

Period 1 title	Study period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	observational

Arm description: -

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Placebo arm

Arm description: -

Arm type	Placebo
Investigational medicinal product name	physiological sodium chloride solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Treatment: 2 - 2.5 mg prednisolone/ kg BW/day or placebo (for 5 days or until clinical manifestation of aGvHD, if prior to day +5).
Taper:1.5 mg/kg BW/ day 6-10, 1 mg/kg BW/day 11-14, 0.5 mg/kg/day 15-19 after administration

Arm title	Prednisolone

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Suspension for injection in pre-filled syringe
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Treatment: 2 - 2.5 mg prednisolone/ kg BW/day or placebo (for 5 days or until clinical manifestation of aGvHD, if prior to day +5).
Taper: 1.5 mg/kg BW/ day 6-10, 1 mg/kg BW/day 11-14, 0.5 mg/kg/day 15-19 after administration

Number of subjects in period 1	observational	Placebo arm	Prednisolone
Started	167	48	44
Completed	130	30	26
Not completed	37	18	18
Consent withdrawn by subject	3	1	1
no information	-	1	-
death	34	15	16
Lost to follow-up	-	-	1
Protocol deviation	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	observational
Reporting group description: -	
Reporting group title	Placebo arm
Reporting group description: -	
Reporting group title	Prednisolone
Reporting group description: -	

Reporting group values	observational	Placebo arm	Prednisolone
Number of subjects	167	48	44
Age categorical Units: Subjects			
Adults (18-64 years) From 65-84 years			
Age continuous Units: years arithmetic mean standard deviation	 49.4 ± 14.12	 52.9 ± 12.64	 53.0 ± 11.62
Gender categorical Units: Subjects			
Female Male	59 108	21 27	15 29

Reporting group values	Total		
Number of subjects	259		
Age categorical Units: Subjects			
Adults (18-64 years) From 65-84 years	0 0		
Age continuous Units: years arithmetic mean standard deviation	 -		
Gender categorical Units: Subjects			
Female Male	95 164		

End points

End points reporting groups

Reporting group title	observational
Reporting group description: -	
Reporting group title	Placebo arm
Reporting group description: -	
Reporting group title	Prednisolone
Reporting group description: -	
Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description: all patients randomized	
Subject analysis set title	Per Protocol
Subject analysis set type	Per protocol
Subject analysis set description: all randomized patients, who fulfilled the key inclusion criteria and received double-blind treatment for at least 3 days (pre-emptive dose of ≥ 2 mg/kg). Patients in the per-protocol population were analyzed as treated	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description: patients were excluded from the safety analysis, because they didn't take any study medication	

Primary: occurence of aGvHD ≥grade 2

End point title	occurence of aGvHD ≥grade 2[1]
End point description: The primary endpoint was defined as the occurrence of aGvHD ≥grade II between time of randomization and 100 days after HSCT. If a death occurs between randomization and 100 days after HSCT in a patient without aGvHD (≥ grade II), then this was also considered as treatment failure, equivalent to an aGvHD (≥ grade II).	
End point type	Primary
End point timeframe: 100 days after HSCT	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Patients who were not randomized were included into the observational study group, this group was not included in the analysis of the primary endpoint

End point values	Placebo arm	Prednisolone	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	48	44	92	
Units: patients with aGvHD ≥grade II	12	11	23	

Statistical analyses

Statistical analysis title	difference between treatment groups at 100 days
Comparison groups	Prednisolone v Placebo arm

Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 1
Method	Cochran-Mantel-Haenszel

Notes:

[2] - efficacy

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Documentation of (S)AEs was done only for the duration of IMP intake (e.g. prednisolon/placebo for 19 days).	
Adverse event reporting additional description:	
Only number of affected subjects available, not number of events.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo	
Reporting group title	Prednisolone
Reporting group description:	
Prednisolone	

Serious adverse events	Placebo	Prednisolone	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 45 (13.33%)	3 / 42 (7.14%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Graft versus host disease in skin			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	1 / 45 (2.22%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swallowing difficult			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary haemorrhage			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations			
Oral herpes			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			

subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Placebo	Prednisolone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 45 (64.44%)	21 / 42 (50.00%)	
Investigations			
C-reactive protein increased			
subjects affected / exposed	2 / 45 (4.44%)	1 / 42 (2.38%)	
occurrences (all)	2	1	
Congenital, familial and genetic disorders			
Aplasia			
subjects affected / exposed	2 / 45 (4.44%)	0 / 42 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 45 (4.44%)	0 / 42 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	0 / 45 (0.00%)	2 / 42 (4.76%)	
occurrences (all)	0	2	
Oedema peripheral			
subjects affected / exposed	0 / 45 (0.00%)	2 / 42 (4.76%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	8 / 45 (17.78%)	4 / 42 (9.52%)	
occurrences (all)	8	4	
Nausea			
subjects affected / exposed	5 / 45 (11.11%)	2 / 42 (4.76%)	
occurrences (all)	5	2	
Vomiting			

subjects affected / exposed	2 / 45 (4.44%)	2 / 42 (4.76%)	
occurrences (all)	2	2	
Abdominal pain upper			
subjects affected / exposed	1 / 45 (2.22%)	1 / 42 (2.38%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 45 (2.22%)	1 / 42 (2.38%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 45 (6.67%)	1 / 42 (2.38%)	
occurrences (all)	3	1	
Cystitis haemorrhagic			
subjects affected / exposed	0 / 45 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	3	
Renal failure			
subjects affected / exposed	1 / 45 (2.22%)	1 / 42 (2.38%)	
occurrences (all)	1	1	
Infections and infestations			
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 45 (2.22%)	1 / 42 (2.38%)	
occurrences (all)	1	1	
Candida infection			
subjects affected / exposed	0 / 45 (0.00%)	2 / 42 (4.76%)	
occurrences (all)	0	2	
Oral herpes			
subjects affected / exposed	1 / 45 (2.22%)	1 / 42 (2.38%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
Oedema			
subjects affected / exposed	2 / 45 (4.44%)	0 / 42 (0.00%)	
occurrences (all)	2	0	
Decreased appetite			
subjects affected / exposed	2 / 45 (4.44%)	0 / 42 (0.00%)	
occurrences (all)	2	0	
Hyperglycaemia			

subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	2 / 42 (4.76%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 October 2009	Protocol version 4
07 January 2010	Protocol version 5
04 August 2011	Protocol verison 6

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33082512